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Safety and Efficacy of Sertraline for Depression in Patients with CHF (SADHART-CHF): A Randomized, Double-Blind, Placebo-Controlled Trial of Sertraline for Major Depression with Congestive Heart Failure

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Abstract

Background—Sertraline, a selective serotonin-reuptake inhibitor (SSRI), has demonstrated substantial mood improvement in patients with post myocardial infarction or with unstable angina. The impact of sertraline on the prognosis and depression of patients with chronic heart failure (HF) and co-morbid major depressive disorder (MDD) is unknown.

Method—This is a prospective, randomized, double-blind, placebo-controlled study designed to assess the safety and efficacy of sertraline in the treatment of MDD in patients with HF. The study is designed also to examine the effects of treating depression on cardiac events and morbidity/mortality in HF patients. Approximately 500 men and women who are ≥45 years of age with current MDD and chronic systolic HF, characterized by left ventricular ejection fraction (LVEF) ≤45% and New York Heart Association (NYHA) class ≥ II comprise the study population. Eligible participants are randomized to either sertraline or placebo for a 12-week acute treatment phase. All patients, regardless of acute treatment phase completion, are followed routinely until the last subject completes 6-month follow-up. Quality of life and certain physiologic parameters, as well as pro-inflammatory and HF biomarkers, that may reflect the impact of sertraline in this particular population, are measured at baseline and at the end of the acute treatment phase.

Randomized Clinical Trial Number: NCT00078286

Conclusion—Because of the high prevalence of depression and its significant adverse impact on prognosis of patients with ischemic heart disease and HF, the SADHART-CHF trial aims to assess the effects of sertraline on response of depression as well as on the cardiac prognosis of patients with HF.

Chronic heart failure (HF) is a major public health problem in the United States, currently affecting more than 3 million Americans with approximate 550,000 new cases diagnosed each year (AHA 2005). HF claims the lives of over 200,000 people in the US annually. Approximately 50% of HF patients die within 5 years and one-year mortality is up to 50% among New York Heart Association (NYHA) class III and IV patients.[1] and [2] In addition, 25% to 50% of hospitalized HF patients are re-hospitalized within 3 to 6 months. The cost of HF-related hospitalization alone is about $7 billion. Total treatment costs for HF, including physician visits, drugs, and nursing home stays were over $10 billion in 1990.

Many factors correlate with mortality in patients with HF. Clinically, the presence of ischemic heart disease (IHD), an audible S3, low pulse and systolic blood pressure, a high NYHA functional class (>II), and reduced exercise capacity or fitness are all associated with increased risk of death.[3], [4] and [5] Increased plasma levels of norepinephrine, renin, and vasopressin and decreased cardiovascular autonomic tone are associated with high risk of death in HF patients as well.[6] and [7] Depression in these patients increases the mortality and rehospitalization risk to a 50–60% prevalence rate.8. The adverse effects of depression on the prognosis of HF is comparable to the impact of aging or ischemic etiology on HF prognosis and is independent of those factors.9

Previous studies have demonstrated that selective serotonin reuptake inhibitors (SSRIs) substantially improve mood in patients with post-myocardial infarction, unstable angina, or other forms of ischemic heart disease (IHD).10 In conjunction, use of those SSRIs are with a generally benign cardiovascular profile, i.e., no deleterious effects on heart rate, blood pressure, left ventricular ejection fraction (LVEF), or ventricular ectopy have been observed. However, it is unknown whether they may improve depression in HF patients with co-morbid major depressive disorder (MDD) and, thereby, improve cardiac outcomes in these patients.

Methods

Trial Design

The SADHART-CHF study is an NIMH sponsored, prospective, randomized, double-blind, placebo-controlled study that is designed to assess the safety and efficacy of sertraline in the treatment of HF patients with MDD. To enhance the generalizability of the findings, study participants are primarily recruited from an academic center (Duke University Medical Center, the study's primary center), and two community hospitals and clinics (Durham Regional Hospital and Alamance Hospital, and their affiliated clinics, the study's satellite sites).

The study includes 2 phases: (1) a 12-week acute treatment phase and (2) a long-term open treatment follow-up phase. The trial incorporates the general governance infrastructure of a phase IIIb clinical trial: administrative and scientific leadership and oversight by: (1) an Executive Committee; (2) a Study Coordinating Center, (3) a Clinical Events Committee (CEC), and (4) a Data Safety and Monitoring Committee (DSMC). An outline of the study is presented in Figure 1

Trial Population and Recruitment

The study population consists of patients who are at least 45 years of age with diagnosis of chronic HF of any etiology. Eligible patients must meet the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for MDD and have a history of chronic

systolic HF characterized by LVEF ≤45% and NYHA class ≥ II. A total of 500 qualified patients are expected to be randomized to one of two treatments arms (sertraline or placebo). Study eligibility criteria are shown in Table 1.

Recruitment—After initial, signed consent, patients with HF from the primary recruiting site (Duke University Medical Center) are screened for depressive symptoms using the Beck Depression Inventory Scale (BDI).11 Patients whose BDI scores are equal to or greater than 10 are given a second consent form to sign followed by the Diagnostic Interview Schedule (DIS) a structured psychiatric interview to assess MDD. Patients recruited from the satellite sites (Community hospitals and their clinics) are approached directly for participation in the trial prior to formal BDI screening.

The difference in initial approaches of potential trial participants between the primary recruiting site and the satellite sites is determined by patient and research staff accessibility. The primary recruiting site is an inpatient service in a tertiary medical center. The number of HF patients who may qualify for depression assessment and possible participation in the trial ranges from 10 to 20 daily. Because the BDI screening is brief and self-administered, it allows the research team to narrow the focus to potential participants that qualify for the structured psychiatric interview. The satellite sites are predominantly outpatient cardiology clinics and the study personnel for those sites are highly experienced psychiatric research nurses. A smaller volume of patients makes it easier and more time efficient to conduct the structured interview in all subjects who consent to participate.

Randomization and Management of Study Drug

Eligible patients are randomized to sertraline or placebo once daily for a 12-week double-blind treatment period. A stratified randomization scheme with permuted blocks and clinical sites as the stratification variable is administered by a centralized computerized interactive voice response system (IVRS).

Initial sertraline dose is started at 50mg and then titrated up biweekly (over a 6 week period) at 50mg incrementally to a 200mg dose maximum. Patients are followed at biweekly intervals. Although the primary plan is to maximize the dose by the end of week 6, for patients who are not able to tolerate the scheduled titration and continue to show depressive symptoms, titration may occur after week 6 until week 10. For those participants unable to tolerate the minimum 50mg dose, a 25mg dose is permitted. For patients who have difficulty tolerating the study drug, and whose side effects are not severe or life threatening, a brief medication taper and re-challenge may be conducted. During the acute treatment phase, study medication compliance and pill counts are assessed.

At the last treatment visit, participants who continue to show depressive symptoms will be evaluated further and study physicians will make patient care recommendations. All patients with continuing depressive symptoms will be referred for treatment by a psychiatrist not affiliated with the study or for follow-up with the participant's primary care physician. The study physician is available on call for questions or concerns during this period.

Long-term Follow Up

All patients, irrespective of 12-week acute study treatment phase completion, are contacted for long-term follow-up until the last participant enrolled completes the 6-month follow-up period. At the end of this acute treatment phase, participants are offered a 30-day sertraline 50mg/day or 20mg/day citalopram prescription depending on the change of the depressive symptoms of those participants and their preference. The anticipated mean long-term open treatment follow-up phase is 2.5 years. During the follow-up period, study personnel contact participants by

phone to gather information on outcome status (clinical events such as visits to the psychiatric service, emergency rooms, or hospitalizations) and vitals status.

Study Endpoints and Assessments

Primary Endpoints—The primary endpoints for the 12-week acute treatment phase are: (1) change in severity of depressive symptoms during acute treatment, as measured by the total score for the 17-item Hamilton Depression Rating Scale (HDRS) and (2) cardiovascular status, a composite score designed to evaluate whether worsening of HF occurred at any point during acute treatment (phase 1) and/or long-term open treatment follow-up (phase 2). Based on the definitions that are listed in Table 2, there are three possible levels of cardiovascular status: (1) improved; (2) unchanged, or (3) worsened.

Key Secondary End Points—Table 3 outlines the detailed assessments and the schedule. The following psychiatric and cardiovascular assessments will provide key secondary endpoints. These measures are selected to evaluate change in functional status and quality of life. Secondary endpoints include 3 binary depression measures: (1) response that is defined as a 50% or greater reduction in the HDRS total score; (2) remission, defined as a HDRS total score less than 8; and (3) patient-reported treatment response, response defined as BDI total score less than 10. Additional secondary endpoints are BDI total score, Clinical Global Impression Scale-Improvement rating by research personnel (CGI-I), Clinical Global Impression Scale-Improvement rating by participants (CGI-I self-rated), Clinical Global Impression Scale-Severity (CGI-S) rating, SF-36 Health Survey scores, rehospitalization, Kansas City Cardiomyopathy Questionnaire (KCQ) scores, and 6-minute walk scores. Paired plasma samples (Baseline and end of 12-week treatment) are collected from approximately 80 consecutively enrolled participants. These samples assess treatment effects on a series of biomarkers. Evaluation of those end points only applies to the acute treatment phase.

Adjudication of Deaths and Primary Cardiovascular Events

An independent Clinical Events Committee (CEC) adjudicates clinical events with an onset following randomization. The CEC is comprised of physicians with therapeutic expertise in cardiology with a sub-specialty in HF. The role of the CEC is to review and code all serious adverse events and clinical events reported during the acute treatment and/or long-term open treatment follow up phases of the study. Two clinicians independently review each event for the purpose of identifying and coding: (1) all-cause deaths and (2) primary cardiovascular events. This process is a critical step in the determination of the elements of the composite cardiovascular status endpoint detailed in Table 2. Events are reviewed and classified according to written procedures and criteria specified in the CEC Adjudication Manual for the SADHART-CHF trial.

All fatal events regardless of etiology are classified as either: (1) successful suicide attempt; (2) non-suicide, non-cardiovascular death; (3) cardiovascular death with unknown cause; (4) cardiovascular death with known cause. Cardiovascular deaths are further sub-classified based on cause of death: sudden cardiac death, circulatory failure death, fatal MI, fatal systemic / pulmonary event, fatal ischemic stroke, or other cardiovascular cause.

Non-fatal events are evaluated to determine whether the event is a primary cardiovascular event. Primary cardiovascular events include exacerbation of HF, acute MI, atrial/ventricular arrhythmia, unstable angina, cardiac syncope, transient ischemic attack (TIA), stroke/ cardiovascular accident (CVA), and/or complications of cardiac medications or cardiac procedures. To meet criteria, the event must have required a hospital admission for a non-elective medical therapy in which the duration is more than 24 hours or results in a change in a calendar day. The exception is exacerbation of heart failure which includes non-elective

hospitalization as well as visits to the emergency room, an urgent care facility, an outpatient clinic, or a hospital with the stay lasts less than 24 hours. Additionally, the cardiovascular event is the primary reason for the medical admission. A hospitalization associated with cardiovascular procedures considered to be elective or scheduled prior to randomization are reviewed but not coded as a primary cardiovascular event.

As part of the adjudication process, the two adjudicators review a narrative description of the event such as patient discharge summary, clinical notes/medical records, and a SAE (serious adverse event) summary (if applicable) related to the event. Each event is coded on a data collection form and returned to the trial statistician who examines the forms for discrepant determinations. Cases with inconsistent event conclusions are resolved in a reconciliation meeting with all CEC members present to discuss the case (s) in order to achieve consensus among adjudicators.

Data Safety and Monitoring Committee

An independent Data Safety and Monitoring Committee (DSMC) reviews the progress of the trial to monitor integrity and to ensure the participant is not compromised. It consists of three independent and recognized leaders with clinical and research expertise in psychiatry, cardiology, and statistics. The DSMC accomplishes its goals through trial protocol review and routine trial monitoring. The DSMC meets every six months to discuss the progress of the study and review a confidential interim data report prepared by the trial statisticians. After each DSMC meeting, the DSMC Chair provides a written recommendation to the study leadership regarding the trial's continuation.

During each meeting, the DSMC members are responsible for the evaluating safety parameters and study integrity indicators, which includes an evaluation as to whether: (1) participants' safety, privacy, and confidentiality are consistently assured by the investigators; (2) additional interim analyses regarding participant's safety are needed ; (3) assessments are administered in a consistent manner and in a way that maintains participants' confidentiality; and (4) issues related to recruitment goals, quality of data, treatment plan adherence, and retention/attrition rates are addressed At the close of each review, the DSMC makes a recommendation as to whether the trial is continued, modified, temporarily suspended, or discontinued. All data in these confidential reports are presented so that randomized treatment is not revealed. If treatment disclosure data is required for the board to make a recommendation regarding the relative risk and benefit of the study, an independent statistical analyst would provide that section of the DSMC report.

Statistical Analyses

Sample Size Consideration—The target enrollment of 500 is based on the number of participants required to test for treatment differences at the change in depression severity and cardiovascular status during acute treatment phase. For each primary outcome, the goal is to determine the required sample size that would provide at least 80% power to test for between-treatment differences assuming an alpha level of 5% (two-sided statistical test).

Based on published results from randomized, placebo-controlled depression trials, the treatment response rate for the HDRS measure is expected to be 60% or greater in the sertraline-treated patients compared to 40% in the placebo condition. For the HDRS outcome measure, a sample size of 214 (107 per arm) is required to detected a 20% difference in treatment response using a test for differences in proportions. Furthermore, this sample size will provide at least 90% power for the planned primary analysis using a random coefficients regression.

For the cardiovascular measure, the expectation is that 36% of the sertraline group will experience a worsening of cardiovascular status compared to 50% in the placebo group. These estimates are based on 3-month mortality and re-admission rates from the Jiang et al. study (2001). For the bi-level composite cardiovascular endpoint, a sample size of 420 (210 per arm) is required to test for 15% differences in proportions of cases with worsening of cardiovascular status.

A target enrollment of 500 (250 per arm) was selected to adjust for a projected early termination rate of 20%. With a recommended sample size of 500, the study will have sufficient power to conduct the primary and supportive analysis of the two primary endpoints collected during the acute treatment phase.

Analytical Methods—The primary analysis of the study is conducted on the intent-to-treat (ITT) cases (all randomized patients) with supportive analyses planned for the "treated" cases (randomized patients who meet the eligibility criteria and receive study medication according to the treatment arm assigned). The statistical plan addresses non-directional hypotheses (two-tailed tests). The level of significance will be set at 0.05 for each statistical test. Random coefficients regression models (RRM) adjusting for the effects of clinical site will be used as a longitudinal data analysis method to examine change in HDRS total scores over an acute 12 week treatment period between the two treatment arms. Major advantages of the random regression approach over a traditional repeated-measures analysis is that the method: 1) provides improved estimates of individual effects; 2) allows for missing data points over time; 3) adjusts for serial correlation (e.g., measurements not equally correlated across time); 4) allows for incorporation of both time-independent and time-dependent covariates; 5) allows for irregular measurement occasions (e.g., does not assume time intervals are equal); 6) provides the ability to model patient-specific time trends (e.g., response to treatment can be individualized); and 7) allows for the assessment of moderator and mediator effects in secondary analyses.

Test for differences of proportions will be used to examine the composite cardiovascular status outcome at the end of acute treatment, 30 days post-acute treatment, and long-term follow up. Chi-square tests will be used to test for overall treatment differences, with a Mantel-Haenszel test performed to examine treatment differences when controlling for clinical site. The primary analyses are conducted initially on the tri-level cardiovascular status outcome, followed by a supplemental analysis of the outcome dichotomized into improved and not improved.

A similar statistical approach will be applied to the secondary endpoints. Secondary exploratory analyses are planned to examine whether treatment outcome is moderated by pre-treatment variables (e.g., etiology of HF) and/or mediated by post-randomization measures (e.g., treatment compliance). All analyses will be performed using SAS 9.1 or higher.12

Discussion

The SADHART-CHF trial is both the largest and the first randomized clinical trial examining effects of an SSRI on depression and cardiac outcome in HF patients with co-morbid MDD.

Necessity of Assessing SSRI Effects on Cardiac Outcome

High rates of depression have been reported in patients with various medical conditions, such as post-MI,[13] and [14] heart failure,[8] and [9] neurological disorders,[15], [16] and [17], endocrinologic/metabolic disorders,18 malignancy[13] and [19] and pulmonary diseases.[8], [20], [21] and [22] Studies of elderly patients with medical illness in the United States indicate that MDD and other depressive disorders are present in 20% to 45% of those ill enough to require hospitalization.[8], [23], [24], [25] and [26] These figures contrast with those for MDD

reported in healthy elders living in the community via the recent Epidemiologic Cachment Area studies that indicates rates of 0.1% to 0.8% in men and 0.6% to 1.8% in women.27 The fate of patients with depression in the medical setting is gloomy; many of these depressive disorders do not resolve once the patient leaves the hospital. For instance, short-term follow-up of a group of elderly male veterans with MDD found that of those patients alive 10 weeks after diagnosis, 64% had persistent MDD and only 18% had gone into a complete remission. 28 Cassem and Hackett found depressed mood in 50% of patients immediately following MI. 29 More than 70% of these patients continued to be depressed one year after initial evaluation. Depression in these cardiac patients is commonly associated with inability to return to work or previous activities, sexual difficulties, and readmission to the hospital. Furthermore, depression is shown as well to significantly affect the medical course of patients with medical conditions and their survival. Depression in post-MI patients and patients with HF is, independent of disease severity and other conventional risks, associated with increased risk for future reinfarction, cardiac arrest, and other mortalities.[14], [9], [30], [31], [32], [33] and [34]

In contrast to the tricyclic antidepressants (TCA), the results of the SADHART trial and several other small studies indicated that SSRIs may be relatively safe among patients with ischemic heart disease.[35], [36] and [37] Sertraline demonstrates a generally benign cardiovascular profile without deleterious effects on heart rate, blood pressure, LVEF, or ventricular ectopy that are seen with TCAs.[38] and [39] SSRIs are associated with substantial improvement in mood ratings after MI or unstable angina and well tolerated by >85% of patients in the study. [40] and [41] Patients receiving sertraline had fewer cardiac events such as death, MI, stroke, worsened angina or onset of CHF as compared with patients taking placebo (Relative risk ratio for having at least one cardiac event was 0.68 with 95% Confidence Interval 0.43–1.09). Although these findings suggest that sertraline may improve cardiac outcome, the study was underpowered to detect treatment effect on cardiac outcome.42 Platelet activities are found to be higher among depressed patients compared to their non-depressed counterparts.43 Serebrauny et. al.44 examined the sertraline effects on platelet markers using a sample subset from the SADHART study. Samples were collected at baseline and at Week 6 from 28 patients who received sertraline and from 36 patients who received placebo. At every time point post baseline, the platelet markers were reduced in the sertraline arm as compared to the placebo arm. The use of antiplatelet regimens between the groups was not different. Influenced by those results, the prescription of antidepressants in cardiology practice surges. Definitive data, however of whether such medications improve cardiac outcome is not yet available.

Study of HF Population

Patients with HF suffer high mortality and morbidity and approximately 50% of HF patients die within 5 years with one-year mortality of up to 50% among NYHA class III or IV patients. [1] and [2] In addition, a 25% to 50% rehospitalization rate occurs within 3 to 6 months of an HF hospitalization. Although there are classes of pharmacological agents which serve the cornerstone of HF treatment and improve survival, clearly depression worsens death rate and rehospitalizations. In our previously reported cohort, although the overall mortality of the study population was 16.2%, the rate was 26.5% for HF patients with MDD compared to the rate of 13.7% for patients whose BDI is < 10. Furthermore, 60.5% of the entire cohort had at least one rehospitalization by 1 year. Similar to the mortality results, the annual readmission rate of patients with MDD was 80.4% compared to 52.3% of the non depressed group.9 Hence, investigation of whether depression treatment may result in reducing cardiac events is of urgent interest. Given the high event rates in HF, the number of patients needed to reach a statistically significant improvement in survival is much lower than the number for patients with acute coronary syndrome. Power calculations indicate that in order to confirm a 20% reduction in

relative risk in depression related cardiac outcome by a randomized trial, a sample size of at least 4000 depressed patients with acute coronary syndrome would be required.44

Etiology of HF under Study

Prior to the evolution of studies examining the association of depression and heart failure, the cardiac population studied was limited to the IHD spectrum. Consequently mechanistic studies and intervention trials have focused on examining the impact of depression in the IHD population. However, further studies among HF patients revealed that the depression prevalence in HF patients and its impact on the prognosis of HF patients are not differentiated between ischemic etiology and non-ischemic etiology.9 Whether the same underlying mechanisms explaining the adverse association of depression and IHD may apply to the adverse association of depression and non-ischemic HF is unknown. Reduced heart rate variability, elevation of platelet activity, and an abnormal proinflammatory process are all present among patients with HF regardless of etiology. The SADAHRT-CHF trial is the first clinical trial to explore whether SSRI treatment will yield similar effects in HF patients with and without IHD.

Translating the Trial into Clinical Practice

The design of the SADHART-CHF trial is tailored to facilitate easy translation into clinical practice should a treatment effect be observed. It is not reasonable to expect a majority of patients with cardiac diseases to visit psychiatrists for depression diagnosis and frequent follow up with antidepressant treatment. These patients have many medical co-morbidities, are taking several different medications, and experiencing compromised physical function. Psychiatric care provided by a psychiatric service is unlikely, especially given the shortage of psychiatric caregivers and limited insurance coverage. In this trial, depression screening and diagnosis are conducted in the ward or in a general cardiologist's office. A well trained nurse or staff personnel conduct the screening and a manual driven diagnostic depression assessment interview. Those personnel are responsible for study medication titration and follow-up of depressive symptoms and other participant performance assessments that are conducted primarily through the telephone with two face-to-face interviews. The primary role of the study psychiatrist is to educate, train, and supervise the study nurses and other staff members who are responsible for the recruitment and follow-up of study participants.

Conclusions

Abundant evidence has solidly confirmed the negative impacts of depression on the prognosis of patients with ischemic heart disease or HF. While studies have found that SSRIs are effective in reducing depressive symptoms and have a benign cardiac profile, research is needed to explore whether such intervention may reverse the adverse impact of depression on cardiac outcomes. The SADHART-CHF study is designed to address this issue. This trial plans to recruit 500 patients with chronic HF and a clinical diagnosis of MDD. Through randomization procedures, half the participants are treated with sertraline and the other half are given placebo for a total of 12 weeks acute treatment. In addition to depressive symptoms, cardiac status will be compared between the sertraline and the placebo groups at the end of the 12-week intervention, during and up to a 5-year follow-up. The comparative results of the 12-week intervention are expected to be available in late 2008.

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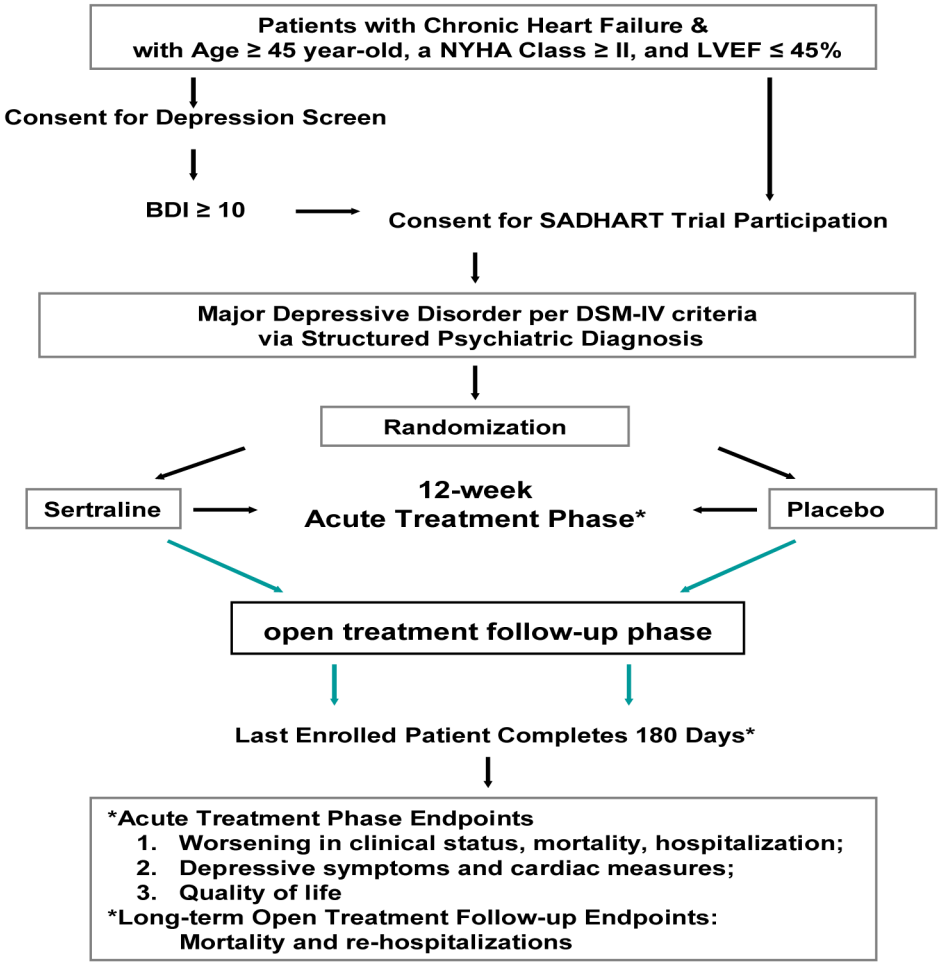

Figure 1.
Flow chart of SADHART-CHF trial

Table 1

SADHART-CHF Eligibility Criteria

Inclusion criteria		Exclusion criteria	
All patients must meet the following criteria:		Patients with any of the following are not eligible for inclusion into the study:	
1.	Male or female, ≥45 years of age.	1.	Significant cognitive impairment, indicated as a MMSE score of 23 or lower.
2.	Chronic congestive heart failure characterized by LVEF ≤45% and NYHA ≥ II.	2.	Alcohol or drug dependence in the last year.
3.	Meets DSM-IV criteria for current MDD.	3.	Severe physical disability (visual, sensory, or motor) that may interfere with psychiatric assessment.
4.	Written informed consent before any study-specific procedure.	4.	History of psychoses, bipolar disorder, and/or severe personality disorders.
		5.	Life-threatening co-morbidity with likelihood of 50% mortality at one year.
		6.	Active suicidal ideations.
		7.	Current use of antipsychotic medications.
		8.	Current use of antidepressant medication(s) at the start of study medication.
			Note: For patients currently using a non-successful antidepressant who wish to discontinue their medication, the following guidelines should be applied:
			• Patients must not be taking a concurrent antidepressant at the start of study medication.
			• Patients currently using a MAOI or fluoxetine must be medication-free for at least 2 weeks prior to the start of the study medication.
		9.	Female patients who have a positive pregnancy test or are lactating. If female patients are of childbearing potential, they must use an effective and accepted means of contraception, such as oral contraceptives or a double-barrier method (condom and diaphragm) to protect against pregnancy.

MDD, major depressive disorder; *MMSE*, Mini-Mental Status Exam; *MAOI*, monoamine oxidase inhibitor

Table 2

Composite Cardiovascular Status

Status	Definition		
Worsened	**Any of the following conditions occur after randomization**		
	Death, regardless of cause		
	Occurrence of one or more of the following primary cardiovascular events: exacerbation of heart failure, acute myocardial infarction), atrial/ventricular arrhythmia, unstable angina, cardiac syncope, transient ischemic attack, stroke/cardiovascular accident, and/or complications of cardiac medications or cardiac procedures.		
	Permanent discontinuation of the Phase 1 double-blind study medication due to cardiovascular reasons		
	Permanent discontinuation of the Phase 1 double-blind study medication because of: (1) refusal to participate, withdrawal of consent or other administrative reasons and (2) at least one of the following occurred during the post-randomization period.		
		•	Primary cardiovascular event on or prior to discontinuation of double-blind medication
		•	Increase of NYHA class on or prior to discontinuation of double-blind medication
		•	Death within 7 days following discontinuation of double-blind medication
Improved	The criteria for (1) “worsened” has not been previously met and (2) at least one of the following conditions occurred at the last assessment completed during the post-randomization period		
		•	Improvement in NYHA functional class
		•	Heart failure status, as determined by the clinician CGI-I score, judged to be moderately-to-markedly improved
Unchanged	Patient is neither improved or worsened		

Primary cardiovascular event: To meet criteria, the event must have required a hospital admission for a non-elective medical therapy in which the duration is more than 24 hours or results in a change in a calendar day. The exception is exacerbation of heart failure which includes non-elective hospitalization as well as visits to the emergency room, an urgent care facility, an outpatient clinic, or a hospital with the stay lasting less than 24 hours. Additionally, the cardiovascular event is the primary reason for the medical therapy.

Table 3

SADHART-CHF Trial Assessment Schedule

Assessment	Screening, Baseline, and Randomization	Acute Treatment (Phase 1)							Long-Term Follow-up (Phase 2)
Visit #	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8–11**
Study Time	**Wk 0 (Day 1)**	**Wk 0 (Day 2/3)**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12**	**Months 6, 12, 24, 36**
Type	FTF	PH	PH	PH	FTF	PH	PH	FTF	PH
BDI	X	X	X	X	X	X	X	X	
DIS	X								
MMSE	X								
HDRS	X		X	X	X	X	X	X	
Demographics	X								
Medical History	X								
Physical Exam	X								
Cardiac Meds	X		X	X	X	X	X	X	
Additional Meds	X		X	X	X	X	X	X	
KCQ	X							X	
Vital Signs	X							X	
6-Min Walk	X							X	
CGI-S	X		X	X	X	X	X	X	
CGI-I			X	X	X	X	X	X	
CGI-I Self-Rated			X	X	X	X	X	X	
CIRS		X							
SF-36		X						X	
SSS		X						X	
Study Med Dose	X		X	X	X	X	X	X	
Clinical Events			X	X	X	X	X	X	X
SAE	X	X	X	X	X	X	X	X	*

BDI: Beck Depression Inventory **CGI-I** Clinical Global Impression Scale – Improvement, clinician version **CGI:** Self Rated Clinical Global Impression Scale – Improvement, patient version **CGI-S:** Clinical Global Impression Scale – Severity, clinician version **CIRS:** Cumulative Illness Rating Scale **DIS:** Modified Diagnostic Interview Scale **FTF**: face-to-face visit **HDRS:** Hamilton Depression

Rating Scale **KCQ:** Kansas City Cardiomyopathy Questionnaire **MMSE:** Mini-Mental Status Exam **PH**: Phone contact **SAE:** Serious Adverse Event **SF-36:** SF-36 Health Survey **SSS:** Social Support Scale

* SAE reporting includes events with an onset within + 30 days of last study medication dose taken during Phase 1.